REMARKS

Status

Claims 19, 20, 25-27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52-56 are pending in this application. With this amendment, Applicants correct a grammatical error in claim 39 and add new claims 57-61. The new claims mirror claims 19, 32, 39, and 46, respectively, with the modification that the new claims recite amino acids 1-52 of SEQ ID NO:1, while claims 19, 32, 39, and 46 recite amino acids 1-51 and 8-41. Support for the new claims can be found, e.g., at page 8, lines 3-11, which describes "an active BAFF-R" having at least about 80, 85, 90, or 95% sequence identity with SEQ ID NO:1 for a full-length BAFF-R or a BAFF-R extracellular domain. Additional support may be found, e.g., at page 5, lines 2-6, which teaches that nucleic acid residues 240-341 of SEQ ID NO:2 correspond to amino acids 8-41 of SEQ ID NO:1. Thus, the "potential transmembrane region at nucleic acid residues 375-459 of SEQ ID NO:2" corresponds to amino acids 53 to 81 of SEQ ID NO:1 and consequently, amino acids 1-52 constitute the extracellular domain sequence.

Priority

Applicants claim domestic priority to U.S. Application Nos. 60/149,378 (filed August 17, 1999), 60/181,684 (filed February 11, 2000), and 60/183,536 (filed February 18, 2000).

The Examiner has rejected Applicants' claim for domestic priority to Application No. 60/149,378 (filed August 17, 1999), stating that the priority application does not adequately describe or enable the claimed pharmaceutical compositions. More specifically, the Examiner alleges that 60/149,378 (1) does not provide descriptive support for polypeptides comprising a sequence that binds to BAFF and is at least 95% identical to amino acids 1-51 of SEQ ID NO:1; and (2) does not enable the claimed pharmaceutical compositions because "the skilled artisan would be forced to make and test to see if one could use the invention as claimed." Office Action of September 29, 2007, at 5. Applicants traverse with respect to both grounds and respectfully request reconsideration of the priority claims in view of the following comments.

The Priority Applications Provide Ample Description of the Claimed Polypeptides

As an initial matter, Applicants respectfully note that the Examiner's characterization of Application No. 60/149,378 is inaccurate; it is simply not true that the "entire provisional specification is drawn to residues 1-52 of BAFF-R and variants thereof." Office Action, at 3. Example 4 describes the immunoprecipitation of BAFF with an Fc-fusion of BAFF-R [BCMA] that comprises amino acids 1-51 (not 1-52) of SEQ ID NO:1. See page 19, line 25, to page 20, line 2 (the construct used in Example 4 was termed pJST538); and page 6, lines 8-11 (pJST538 comprises nucleic acids 1-153 of BAFF-R [encoding amino acids 1-51 of SEQ ID NO:1]). These passages demonstrate that the experimental results described in this application include data

obtained using a BCMA-Fc fusion comprising amino acids 1 to 51. Moreover, these passages indicate that applicants were in possession of a fragment of SEQ ID NO:1 encoding amino acids 1 to 51 at the time these experiments were carried out. The fact that the fragment was used to create an Fc fusion protein does nothing to negate this possession -- or the written description of the fragment itself.

Example 4 is one of several passages supporting Applicants' position that each of the priority documents, viewed as a whole, provides ample support for polypeptides comprising an amino acid sequence that binds to BAFF and is at least 95% identical to amino acids 1 to 51 of SEQ ID NO:1. The Federal Circuit has repeatedly stated that the specification need not provide literal support for claim terminology:

> "[T]he patent specification must describe an invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented what is claimed. We have cautioned, however, that the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue." KAO Corp. v. Unilever United States, Inc., 441 F.3d 963, 967-68, 78 USPQ2d 1257, 1260 (Fed. Cir. 2006) (internal quotes omitted).

Each of the priority documents meets this standard. Application No. 60/149,378 states,

> "the invention provides chimeric molecules comprising BAFF-R [BCMA] polypeptide fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises a BAFF-R fused to a Fc region of an immunoglobulin or an epitope tag sequence." Page 5, lines 11-14.

As noted above, the BAFF-R-Fc fusion protein employed in Example 4 comprises amino acids 1-51 of SEQ ID NO:1. See page 19, line 25, to page 20, line 2; and page 6, lines 8-11. The application also discloses an active BAFF-R having at least about 80, 85, 90, or 95% sequence identity with SEQ ID NO:1 for a full-length BAFF-R or a BAFF-R ECD (extracellular domain) sequence. Taken together, these passages provide unambiguous support for the claimed polypeptides.

Support for the claimed polypeptides is also found in the second and third priority documents. For exemplary support in Application No. 60/181,684, see page 4, lines 7-10; page 5, lines 9-13; page 6, line 31, to page 7, line 5; and page 18, lines 1-10. For exemplary support in Application No. 60/183,536, see page 4, lines 9-12; page 5, lines 9-13; page 6, line 33, to page 7, line 7; and page 18, lines 4-13.

Applicants also note that the Examiner's rejection of the priority claim for allegedly inadequate written description does not apply to new claims 57-61, which relate to sequences that are at least 95% identical to amino acids 1-52 of SEQ ID NO:1. As noted above, the Examiner has previously acknowledged that Application No. 60/149,378 provides support for "residues 1-52 of BAFF-R and variants thereof."

The Priority Applications Fully Enable the Claimed Pharmaceutical Compositions

The Examiner's has also rejected Applicants' priority claim to Application No. 60/149,378 because it allegedly lacks enabling support for the claims. The Examiner states that Application No. 60/149,378 does not contain in vivo data and does not

establish a nexus between in vitro and in vivo activity. The Examiner also states that BAFF is a co-stimulator and that B cell regulation is complex and controlled at many points by different cytokines. The Examiner concludes that the skilled artisan would be forced to make and test to see if one could use the invention as claimed. The Examiner cites In re Kirk and Petrow, 376 F.2d 936, 153 USPQ 48 (CCPA 1967) for the proposition that a patent disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use.

Applicants note that the Examiner's rejection of the priority claim for alleged lack of enablement does not apply to Application Nos. 60/181,684 and 60/183,536. These priority applications each provide data that renders the rejection moot. Example 8, e.g., shows that BCMA-Ig reduces B-cell numbers in vivo. See pp. 20-23 of Application No. 60/181,684 and pp. 21-24 of Application No. 60/183,536.

Moreover, Applicants maintain that Application No. 60/149,378 fully enables the claimed methods. As discussed below, Applicants submit that the Examiner has not met the PTO's burden under In re Angstadt, 537 F.2d 498 (CCPA 1976). And even if the Examiner had met that burden, Applicants now rebut the prima facie case by presenting evidence of enablement.

As an initial matter, Applicants respectfully submit that the Examiner has mischaracterized the enablement standard. In re Kirk and Petrow has no relevance to the instant application. The specification at issue in that case was insufficient because

it did not disclose any specific utility; the application merely asserted that the claimed compounds had "biological activity" and "biological properties." To use the compounds claimed by Kirk and Petrow, the skilled artisan would need to test a potentially infinite number of possible uses. Thus, when the CCPA noted critically that "experimentation would be necessary to determine actual uses - or possible lack of uses - of the compounds," it was referring to the fact that the specification's statements regarding usefulness were "so general as to be meaningless." 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967). The court did not say, as the Examiner would have it, that a disclosure is insufficient if experimentation is necessary to confirm a specifically disclosed use. Indeed, other cases explicitly reject such a formulation of the enablement standard.

The proper test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498 (CCPA 1976). The Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. Id. The possibility of inoperative embodiments does not prove lack of enablement. Atlas Powder Co. v. E.I. duPont de Nemous & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). "Without undue experimentation or effort or expense the combinations which do not work will be readily discovered and, of course, nobody will use them and the claims do not cover them." In re Angstadt, 537 F.2d at 504. Moreover, trial and error

experimentation is not necessarily undue. See, e.g., In re Wands, 858 F.2d 731 (Fed. Cir. 1988) (concluding that screening many hybridomas to find the few that fell within the claims was not undue experimentation).

Applicants respectfully submit that the Examiner has not met the burden articulated by In re Angstadt. The Examiner cites to the complex regulation of the immune system by different cytokines as the reason that the specification is not enabling. However, it was well-known in the art in August 1999 that the immune system can be successfully modulated by methods that target single immunoregulators, including TNF family members. For example, Applicants previously cited Moreland et al., which shows that administration of soluble TNF receptor (etanercept) significantly reduces disease activity in patients with active rheumatoid arthritis. The Examiner relies on Schneider et al. (previously submitted) to show that CD40L is important for B cell survival, proliferation, isotype switching, and differentiation, and the interaction of OX40 and OX40L is necessary for the differentiation of activated B cells into high Ig-producing cells. However, the CD40L and OX40L references cited by Schneider et al. confirm that B cell regulation may be modulated by disrupting a single ligand:receptor interaction. See van Kooten et al., Curr. Opin. Immunol. 9:330-337 (1997); Stuber et al., J. Exp. Med. 183:979-989 (1996) (copies of both attached). Thus, one of skill in the art at the August 1999 priority date of this application was aware that even though a number of

different molecules regulate B cells, the immune system may be successfully manipulated by targeting individual signals.

The Examiner responds to this argument by urging that because the TNF family is pleiotropic and BAFF is "different from other TNF family members," these examples of successful manipulation of B cells by targeting other single molecules still would not allow the skilled artisan to predict the in vivo effect of administering a BCMA fragment; i.e., Applicants still haven't proven that the claimed methods work. However, the specification and knowledge in the art need not prove that BCMA administration is 100% effective. Under In re Angstadt, the disclosure is presumptively enabling; the burden is on the Examiner to give reasons to show that any experimentation would be undue. Applicants do not offer Moreland et al., Schneider et al., van Kooten et al., and Stuber et al. to prove that BCMA administration will be effective or to establish that the skilled artisan could conclusively predict that the claimed methods will work without any experimental confirmation. Rather, these references are submitted to demonstrate that, contrary to the Examiner's contention, the fact that B cell regulation is complex does not by itself establish that undue experimentation would be required for the skilled artisan to manipulate B cells by inhibiting a single regulatory signal. What these references prove is that the Examiner has not met the burden of establishing undue experimentation as articulated in In re Angstadt.

Moreover, even if the Examiner had met the burden of giving reasons why Application No. 60/149,378 is not enabling (and she has not), there is ample evidence in the record to show that the skilled artisan could in fact practice the claimed methods without undue experimentation, thus rebutting any prima facie case made the Examiner. Under In re Brana, post-filing data may be used to prove that the disclosure was in fact enabling when filed. 51 F.2d 1560, 1566-67 & n.19 (Fed. Cir. 1993). See also Gould v. Quigg, 822 F.2d 1074, 1078 (Fed. Cir. 1987) ("factual evidence directed to the amount of time and effort and level of knowledge required for practice of the invention from the disclosure alone . . . can be expected to rebut a prima facie case of nonenablement."). Applicants' own later filings demonstrate that Application No. 60/149,378 was enabling as filed. As noted above, Application Nos. 60/181,684 and 60/183,536 show, e.g., that BCMA-Ig reduces B-cell numbers in vivo. See pp. 20-23 of Application No. 60/181,684 and pp. 21-24 of Application No. 60/183,536. Moreover, Huntington et al. states that BCMA-Fc administration reduces B cell numbers and immunoglobulin levels in murine models of autoimmune disease. International Immunity 18:1473-1485 (2006), p.1477 (Fig. 2 legend: "Treatment with hBCMA causes B cell loss and inhibits antigen-specific and total Ig production"; copy attached). Each of these references demonstrates that the skilled artisan did in fact perform the claimed methods by following the teachings provided in Applicants' August 1999 priority application with no more than routine experimentation. Any one of them alone would suffice to prove enablement. See

Dolbear v. Am. Bell Tel. Co., 126 U.S. 1, 5365, 8 S. Ct. 778, 7832, 31 L. Ed. 863 (1888) ("when the question is whether a thing can be done or not, it is always easy to find persons ready to show how not to do it. If one succeeds, that is enough, no matter how many others fail.") (citations omitted). Thus, as in In re Brana, even if the Examiner had made a prima facie case of nonenablement, "applicants proffered sufficient evidence to convince one of skill in the art" that the disclosure is enabling.

In view of the foregoing remarks, Applicants submit that each of the priority applications (60/149,378, 60/181,684, and 60/183,536) describes and enables the claimed invention. Accordingly, Applicants request that the Examiner reconsider the priority claim and grant priority to August 17, 1999.

Novelty

The Examiner has rejected claims 19, 20, 26, 27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52-56 under 35 U.S.C. § 102(b) and claim 25 under 35 U.S.C. § 102(a) as allegedly anticipated by WO/00/40716. In view of the foregoing remarks with respect to priority, Applicants submit that each claim in the instant application is entitled to priority to U.S. Application Nos. 60/149,378 (filed August 17, 1999), 60/181,684 (filed February 11, 2000), and 60/183,536 (filed February 18, 2000) as well as to PCT/US00/22507 (filed August 16, 2000).[1] Each of the three provisional priority

1 The PCT priority application was filed less than a year after the publication date of WO/00/40716 and thus, that reference cannot serve as prior art under 35 U.S.C. §102(b).

applications predates the July 13, 2000, publication date of the reference. Thus, without comment as to the allegation that the claims read on the teachings of WO/00/40716, Applicants submit that the rejections over this reference are moot and request that they be withdrawn.

The Examiner has rejected claims 19, 20, 25, 26, 27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52-56 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,475,987. Applicants traverse.

U.S. provisional application 60/132892, from which U.S. 6,475,987 claims priority, does not contain any disclosure at all relevant to the pending claims. It describes only the TALL-1 (BAFF) ligand and does not describe any receptors to this ligand. Thus, even if U.S. 6,475,987 contains relevant disclosure, and Applicants do not agree that it does, it would not be entitled to any date prior to its May 5, 2000.

In view of the remarks set forth above with respect to priority, Applicants submit that each of the pending claims is entitled to priority to U.S. Application Nos. 60/149,378 (filed August 17, 1999), 60/181,684 (filed February 11, 2000), and 60/183,536 (filed February 18, 2000). Thus, without comment as to the allegation that the claims read on the teachings of U.S. 6,475,987, Applicants submit that the rejection based on this reference is moot and request that it be withdrawn.

The Examiner has also rejected claims 19, 20, 26, 27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52-56 under 35 U.S.C. §102(e) as allegedly anticipated by

U.S. Patent Application Publication 2003/0148445. In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to priority to U.S. Application Nos. 60/149,378 (filed August 17, 1999), 60/181,684 (filed February 11, 2000), and 60/183,536 (filed February 18, 2000). Each of the three priority applications predates the reference, which was published on August 7, 2003, filed August 9, 2002, and claims priority to a provisional application filed on May 1, 2000. Thus, without comment as to the allegation that the pending claims are anticipated by U.S. 2003/0148445 or the allegation that U.S. 2003/0148445 is entitled to the benefit of its May 2000 priority application, Applicants submit that the rejection over this reference is moot and request that it be withdrawn.

Enablement

The Examiner maintains the enablement rejection under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claims. While acknowledging enablement of a pharmaceutical composition comprising a polypeptide comprising residues 1-51 of SEQ ID NO:1 that binds to BAFF, the Examiner states that the specification does not enable a pharmaceutical composition comprising a polypeptide comprising (1) residues 8-41 of SEQ ID NO:1; or (2) an amino acid sequence that binds to BAFF and is at least 95% identical to 1-51 or 8-41 of SEQ ID

NO:1. Applicants respectfully disagree and request that the enablement rejection be reconsidered in view of the following remarks.

The specification enables polypeptides comprising amino acids 8-41 of BCMA

Applicants maintain that the specification as filed fully enables a pharmaceutical composition comprising a polypeptide comprising residues 8-41 of SEQ ID NO:1. Applicants respectfully submit that the Examiner has not met the burden articulated in In re Angstadt for a showing of undue experimentation. Moreover, even if the Examiner had satisfied that burden, Applicants now present evidence of enablement sufficient to rebut any prima facie case made by the Examiner.

As noted above with respect to priority, the Examiner has the initial burden of giving reasons, supported by the record as a whole, why undue experimentation would be necessary for the skilled artisan to make and use the claimed invention. In re Angstadt, 537 F.2d 498 (CCPA 1976). The Examiner has not met that burden here. The original rejection of residues 8-41 was grounded merely on the Examiner's assertion that "there is no activity demonstrated for the peptide of residues 8-41 of SEQ ID NO:1." Office Action of February 14, 2006, at 8. However, the Federal Circuit has explicitly stated that working examples are not required for enablement. In re Strahilevitz, 668 F.2d 1229, 1232 (Fed. Cir. 1982). "The mere fact that something has not been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." Gould v. Quigg, 822 F.2d 1074, 1078 (Fed. Cir.

1987). In the language of In re Angstadt, even if experimentation would be necessary to confirm the activity of residues 8-41, the Examiner has provided no reason that such experimentation would be undue. 537 F.2d at 504. Thus, the Examiner's observation that the specification does not contain data proving that residues 8-41 have activity does not meet the PTO's burden to provide reasons why the specification is not enabling.

In the absence of even a prima facie case of non-enablement in the Office Action of February 14, 2006, Applicants bore no burden to offer evidence of enablement in their reply. However, in the interests of putting the matter to rest, Applicants noted in the reply of June 14, 2006, that the specification demonstrates that the binding domain is localized within residues 1-51 and teaches that residues 8-41 form the cysteine-rich domain (CRD). In view of knowledge in the art that the CRD is "the canonical motif" of the TNF receptor superfamily [see Smith et al., Cell 67:959-962 (1994), previously submitted], the skilled artisan would thus expect residues 8-41 to bind BAFF.

Still bearing the burden under In re Angstadt to provide reasons, supported by the record as a whole, why the specification is not enabling, the Examiner now merely criticizes Applicants' comments regarding Smith et al. Even if the Examiner's criticism held merit, it still does not satisfy the PTO's burden. Under In re Angstadt, the specification is presumptively enabling. Applicants bear no burden until and unless the Examiner makes a prima facie case that the specification is not enabling. Rebutting

Applicants' supplemental and legally unnecessary remarks regarding the skilled artisan's expectations about the CRD would merely bring the matter back to the Examiner's original and legally insufficient observation that the specification does not demonstrate experimentally that residues 8-41 have activity. The Examiner still has not provided reasons why any required experimentation would be undue.

Moreover, the Examiner mischaracterizes Smith et al. and the art in general. The Examiner's response to Applicants' discussion of Smith et al. is that (1) the reference "admits" considerable variation in the size and number of CRDs among TNF receptor family members; (2) the receptors of Smith et al. have multiple repeats; and (3) there is no teaching in Smith et al. that the "canonical motif" is the minimal ligand-binding sequence of the extracellular domain. Office Action of September 29, 2006, at 6-7.

Applicants respectfully disagree with point (3) and further, submit that points (1) and (2) do not diminish the skilled artisan's expectation that the BCMA CRD (residues 8-41) binds BAFF. Smith et al. teaches that the "cysteine-rich pseudorepeats" (i.e., the CRDs) are the sites of ligand-binding in this family of receptors. The reference describes a "unifying picture of the prototypic interaction between ligands and receptors" in which three copies of a receptor bind a ligand trimer, with the receptor CRDs "forming an elongated array that lies in the interfaces between each pair of the three ligand protomers." Page 960, left column. Variations in the size and number of repeats does

not change the basic model that the CRD is the site of binding. Similarly, the observation that the claims are "drawn to an apparently single motif," while the "receptors of Smith et al. have multiple repeats," does not suggest that the claimed polypeptides would not bind BAFF. The claims require only a single repeat because BCMA has only a single repeat. In view of the general model that CRDs are the ligand-binding site, Applicants' showing that BCMA binds BAFF implies that this single repeat is sufficient.

Moreover, in spite of the fact that the Examiner has not met the burden on the PTO under In re Angstadt, Applicants now provide evidence sufficient to rebut any allegation that the specification does not enable polypeptides comprising residues 8-41. As noted with respect to priority, post-filing data may be used to prove that the disclosure was in fact enabling when filed. In re Brana, 51 F.2d 1560, 1566-67 & n.19 (Fed. Cir. 1993); Gould v . Quigg, 822 F.2d 1074, 1078 (Fed. Cir. 1987). In a 2003 Nature article, Liu et al. describe the crystal structure of TALL-1 [BAFF] bound to "eBCMA" (residues 5-43). Nature 423:49-56 (2003) (copy attached). All of the amino acids in BCMA that Liu et al. mentions in describing the BAFF:eBCMA structure lie within residues 8-41: the six cysteines at positions 8, 21, 24, 28, 37, and 41 form three disulfide bridges and the nine residues in BCMA that are involved in the BCMA:BAFF interaction are at positions 13, 15, 17, 18, 19, 22, 26, 27, and 34. Page 50, right column, and page 52, right column. These results necessarily imply that amino acids 8-

41 are sufficient for BAFF binding and thus indicate that the specification was enabling as filed.

The specification enables the claimed sequence variants

Applicants maintain that the specification as filed fully enables a pharmaceutical composition comprising a polypeptide comprising a sequence that binds to BAFF and is at least 95% identical to amino acids 1-51 or 8-41 of SEQ ID NO:1.

As an initial matter, Applicants note that "a sequence that is 95% identical to X and has activity A" is a standard claim formulation that the PTO has repeatedly approved. Hundreds of issued patents contain claims to sequences having a specified activity and some percent identity (often far less than 95%) to a disclosed sequence. The PTO's own Guidelines endorse a claim to "A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B" as adequately described by a specification that only "exemplifies" SEQ ID NO:3. Written Description Guidelines, Example 14. Although these Guidelines focus on the written description requirement, Applicants submit that the PTO would not praise a non-enabling specification as an example of adequate written description without even mentioning the possibility of an enablement problem.

Moreover, Applicants submit that the Examiner has again mischaracterized the enablement standard. The Examiner repeatedly states that sequence variants retaining BAFF-binding activity "cannot be predicted" and "can only be empirically determined" as

"there is no guidance as to what residues are critical for binding." Office Action of September 29, 2006, at 6-7. The Examiner again cites In re Kirk and Petrow for the proposition that "the courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use." Id. at 6.

Applicants respectfully submit that the case law flatly contradicts the Examiner's characterization of the enablement standard. In the interest of brevity, Applicants refer to their discussion of the enablement standard in the context of the priority claim. In short, In re Kirk and Petrow does not apply to the instant application. The quoted passage refers to a specification that fails to disclose any specific utility, potentially forcing the skilled artisan to test all possible uses. Moreover, In re Angstadt explicitly rejects the notion that enablement requires predictability. 537 F.2d at 503.

> "If . . . the disclosure must provide 'guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction, whether the claimed product will be obtained,' as the dissent claims, then all 'experimentation' is 'undue,' since the term 'experimentation' implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act." (emphasis in the original).

See also In re Wands, 858 F.2d 731 (Fed. Cir. 1988) (concluding that screening many hybridomas to find the few that fell within the claims was not undue experimentation).

Applicants submit that the specification readily complies with the enablement standard articulated by In re Angstadt and In re Wands. In the interest of brevity, Applicants incorporate the remarks on this issue from their previous replies. See

Amendment and Reply of June 14, 2006, at 18-20; Amendment and Reply of July 18, 2005, at 21-27. As discussed in greater detail in the earlier submissions, Bowie et al. teaches that "proteins are surprisingly tolerant of amino acid substitutions" and that a systematic approach (with no guidance as to which residues are critical for activity) yields a high fraction of functional variants.

Moreover, even though In re Angstadt and Bowie et al. make clear that predictability is neither legally nor technically necessary, respectively, the skilled artisan would have guidance as to which residues in BCMA are likely to be important for BAFF binding. The human and mouse BCMA sequences were both known in the art. See Madry et al. (previously submitted). As Applicants were the first to discover that BCMA binds BAFF, the art had not previously noted which residues in human BCMA are likely to be important for BAFF binding. However, the skilled artisan would know to compare the mouse and human sequences to identify amino acids that are conserved, and thus likely to be important for activity.

In view of Bowie et al. and Madry et al., the skilled artisan would expect to identify functional variants through no more than routine effort. Even if some variants prove not to bind BAFF, "[w]ithout undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." 537 F.2d at 219.

In summary, Applicants' disclosure, considered in view of knowledge in the art, satisfies the enablement standard articulated by In re Angstadt and In re Wands. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that all outstanding rejections have been overcome. Accordingly, reconsideration of claims and expedited allowance are earnestly requested. The Examiner is urged to call the undersigned with any questions at (617) 452-1669.

Applicants believe that any fee required for the entry of this amendment is accounted for by the accompanying Petition for Extension of Time. However, in the event of an error, please grant any additional extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 28, 2007

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